Use of automated blood pressure measurements in clinical trials and registration studies: data from the VALTOP Study

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Background **Auscultatory measurement of office blood pressure (BP) by mercury sphygmomanometers (AuscBPM) is still the gold standard in clinical trials and registration studies for antihypertensive drugs. The increasing availability of accurate automated oscillometric BP measuring devices has offered new perspectives in this field, although their usefulness in drug studies has not been systematically tested yet.**

Methods **During the course of Valsartan 320 mg EU Registration Study we used an electronic automated oscillometric BP measuring device (eBPM) as an alternative to conventional AuscBPM. Altogether 3776 patients were randomized into a double-blinded actively controlled parallel group study in 303 centers, and 54 422 BP readings were recorded by the validated, electronic, automated oscillometric device OMRON 705IT with digital printouts. Terminal digit preference and preference at therapeutic cutoff points were evaluated. The data were compared with the results of an earlier valsartan study similar in design but based on conventional AuscBPM. Furthermore, based on a simulation, four strategies for automated BP measurement with varying number of office readings (3–5) were analyzed to define an optimal method to collect BP at office visits.**

Results **eBPM eliminated terminal digit preference and dramatically reduced preferences for therapeutic cutoff points as compared with earlier valsartan trials with conventional AuscBPM. However, even with eBPM a minor bias with the therapeutic cutoff value was observed probably because of an observer bias during data documentation. The within-patient variability of three measurements sequentially taken at each visit was similar to other strategies including more measurements.**

Conclusion **On the basis of our data, we suggest that eBPM is a suitable alternative to AuscBPM in clinical trials and registration studies, and may carry specific advantages. Automatic data transfer of recorded values to electronic patient files may further minimize observer bias. Manufacturers should consider such findings for the development of professional devices.** ***Blood Press Monit*** **15:188–194 © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Keywords: clinical trials, electronic blood pressure measurement, observer bias, professional devices, registration studies

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Introduction

The use of auscultatory readings by a mercury sphygmomanometer (AuscBPM) is still the gold standard for the measurement of office blood pressure (BP) in clinical trials. The majority of available epidemiological data on population studies were collected by this method. These data have served as basis for international guidelines on BP diagnosis, prognosis and treatment by scientific bodies. Even when AuscBPM is used according to strict recommendations, such as those released by the American Heart Association or the European Society of Hypertension [1,2], its application is limited by inaccuracies related to the measurement technique itself and by the observer bias [3,4]. In fact, the AuscBPM method requires regular training and retraining of observers, and most physicians do not routinely perform correct BP measurements [5–8]. An important source of observer bias is terminal digit preference and preferences in relation to diagnostic/therapeutic cutoff values [9–12] when diagnosing hypertension, recruiting patients in a trial or evaluating response to treatment.

Furthermore, the use of AuscBPM is increasingly limited by the more and more frequent restrictions to marketing of mercury-based diagnostic devices implemented in many European countries because of mercury toxicity [13], which has made the search for alternative solutions to mercury manometers a highly relevant issue in recent years. Among these alternatives, electronic BP measuring devices based on the use of the oscillometric technique are increasingly being adopted. Their easy application and the constant improvement in their technical features over the last few years have led to a progressive diffusion of automated BP measurement in a clinical setting and in

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clinical trials as a suitable alternative to AuscBPM [1]. However, a limited number of automated devices have been designed for use in the doctor's office and only a few of them have been validated for this application. Moreover, no electronic method for BP measurement (eBPM) has been until now recommended in the frame of clinical trials.

The possibility of using eBPM in trials has been indeed considered by the centralized European drug regulatory body, European Medicinal Evaluation Agency and by one of its committees, the CPMP (Committee for Proprietary Medicinal Products), in their guidelines on 'clinical investigation on medicinal products in the treatment of hypertension' (CPMP/EWP/238/95 rev.1. Nov.1997). Their statements have opened the way to use of electronic oscillometric devices for BP measurement in clinical trials aimed at obtaining drug registration at CPMP, provided that such devices are validated according to either Association for the Advancement of Medical Instrumentation, British Hypertension Society or the international protocol proposed by the European Society of Hypertension working group on BP monitoring. From a statistical point of view, accurate automatic readings might help reducing interobserver bias during BP measurements, thus increasing their precision.

On the basis of the above considerations, different randomized clinical studies, such as the Hypertension Optimal Treatment Trial or the recently published Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), made use of eBPM in the physician's office, whereas eBPM has been used in trials for registration filing in the US [14]. Until now, however, no studies have addressed the pros and cons of eBPM in this setting.

The aim of this study was to specifically explore this issue, in the frame of Valsartan 320 mg EU Registration Study (VALTOP), by addressing the following issues:

(1) Whether electronic BP can be used as an alternative to conventional BP.
(2) The influence of BP measurement method on terminal digit preference and therapeutic cutoff point preference, using data from VALTOP (eBPM) and a Valsartan Study of similar design [Valsartan/HCTZ versus Amlodipine in STage II hypertensive patients (VAST)] that used conventional BP [15].
(3) Strategies with varying numbers of BP readings to define an optimal method for office BP measurement.

Materials and methods

VALTOP Study

The BP effects of two different doses of valsartan (160 and 320 mg) were studied in a mild–to-moderate hypertensive population – VALTOP Study. Altogether 3776 patients were randomized, between 23 September 2003 and 10 January 2005, into this double-blinded randomized actively controlled parallel group study carried out in 303 centers located in 24 countries from Europe to Latin America. In each patient, a 2-week washout screening phase was followed by a 4-week open label run-in phase (160 mg) and subsequently by a 4-week double-blinded randomized phase (comparing valsartan 160 and 320 mg).

At the start of the open-label period (visit 2), all the patients needed to have a mean seated diastolic blood pressure (DBP) at least 95 and 109 mmHg or less.

At the randomization visit, the patients were stratified into two groups, that is, responders (DBP < 90 mmHg) and nonresponders (DBP ≥ 90 mmHg) to the 160 mg dose. Study objectives were to assess the BP lowering effects of valsartan (160 and 320 mg) after 4 weeks of treatment, separately in responders (DBP < 90 mmHg at randomization) and in nonresponders, and in the whole group of patients.

Blood pressure measurement

During the study, the patients' BP was measured by a validated, electronic, automated oscillometric device (OMRON 705IT, OMRON HEALTH CARE, Kyoto, Japan) in all study centers [16]. The device was selected based on the fact that it was validated through an international protocol, was easy to use, provided a printable BP output, was relatively cheap, was equipped with a memory capable for storage of 2–3000 readings and there was a global coverage by the supplier.

To decrease BP readings variability and other known sources of bias during BP measurement, methods for automated BP assessment were strictly defined. Training was provided before the start of the study, and regular updated information was provided during the course of the study.

In detail: (i) Sitting and standing BPs were measured at each visit. BP measurements were taken at trough (24 ± 3 h post dose), after the patient had been sitting for 5 min. Every effort was made to have the same investigator perform BP measurements in the same patients at each visit by using the same equipment. (ii) During BP measurement, while sitting on a chair, patients had to keep their feet flat on the floor and their arm supported, so that the bottom of the cuff was at the heart level. The bottom of the cuff was kept approximately 1–2 cm above the elbow, and the green label on the cuff lay over the brachial artery on the inside part of the arm. Patients were asked to relax the arm when their BP was measured, keeping the palm of the hand turned upward. The investigator had to make sure that there were no kinks in the air tubing. (iii) Patients were not allowed to move or speak during the measurement. (iv) The investigator was required to check the size of the cuff and use the correct

cuff size. The bladder of the cuff had to be long enough to encircle at least 80% of the arm. (v) At study entry BP was measured in both the arms. If there was a clinically significant BP difference between the arms [$\geq$ 10 mmHg in systolic BP (SBP) and/or $\geq$ 5 mmHg in DBP], the arm with the higher BP was used. If there was no clinically significant BP difference between the arms, the non-dominant arm was used. In any given patient, the same arm was used in all subsequent visits. The arm used in each visit was identified and reported in the visits source documentation. (vi) At each visit, sitting BP was measured three times, at 1–2-min intervals. Standing BP was measured only once, within 2 min after the last sitting BP measurement (data not reported in this study). The mean of the three sitting BP measurements was taken as the value of sitting clinic BP for that visit.

VAST Study

Male or female patients who were 18 years of age with moderate hypertension defined by a mean seated SBP (MSSBP) of 160 mmHg at visits 1, 2 and 3 for untreated patients. Patients on current antihypertensive treatment who remain uncontrolled (i.e. MSSBP $>$ 140 mmHg) on their present regimen and who had a BP of 160/95 mmHg at visit 1 and a proven medical history of moderate hypertension. Pretreated patients must meet the criterion of a MSSBP of 160 mmHg at visit 3.

The primary efficacy variable for study 2 was the change in the mean SBP to endpoint (week 24).

Blood pressure measurement in VAST Study

Sitting and standing BP was recorded. The arm in which the highest sitting pressures were found was the arm used for all subsequent readings throughout the study. If there was a discrepancy between the arms regarding the highest systolic and diastolic value, the arm with the highest mean BP was used according to the following formula: mean BP = DBP + [(SBP-DBP)/3]. All attempts were made to have the same investigator obtain BP readings in each individual patient at each visit at the same time of the day with the same equipment.

Using a calibrated standard sphygmomanometer with the appropriate size cuff, arterial BP determinations were made in accordance with the American Heart Association Committee Report on BP determination. With the arm supported at the level of the heart, systolic pressure was recorded when the initial sound was heard (phase I of the Korotkoff sound) whereas diastolic pressure was recorded at the disappearance of the sound (phase V of the Korotkoff sound). At each study visit, after having the patient in a sitting position for 5 min, SBP/DBP was measured three times. The repeat measurements were to be made at 1-2-min intervals. The cuff was deflated at a rate not greater than 2 mmHg/s. Investigators were instructed to ensure that the three measurements agreed by $\pm$ 5 mmHg. No up-and-down-rounding was allowed. If the measurements did not agree they were repeated after 5 min at rest. The mean of all three sitting measurements was used for the study's specific procedures.

Variability of measurements and optimal method for collecting blood pressure readings

Locked data from the clinical database of the VALTOP Trial were used to perform some simulation aimed at identifying the best strategy to reduce the variability between consecutive BP measurements within a patient. Four strategies were considered, which were respectively based on:

(1) three measurements, but leaving out the highest and lowest ones,
(2) three consecutive measurements,
(3) four measurements, but leaving out the first one, and
(4) five measurements, but leaving out the highest and the lowest ones,

as in the VALTOP Study where only three repeated measurements were performed, it was not possible to estimate the real variance of the further measurement in strategy 3/4. For the simulation it was assumed that the variance of further measurements is the same as the variance of the first three measurements. To assess the above four strategies, raw DBP data from VALTOP were analyzed using a mixed-effect linear model to derive adjusted means and variances of DBP. Subsequently, a similar mixed-effect linear model was fitted to obtain individual DBP for baseline and endpoint visits. Finally, for each strategy the measurements were simulated for the whole population, and the standard deviations (SDs) of the BP readings (at each visit) were estimated and compared, to evaluate the efficiency of strategies 1–4 in reducing BP variability. Simulations were performed to obtain 1 000 000 samples using SAS version 8.2 (SAS Institute Inc., Cary, North Carolina, USA), to ensure a precision of 10^{-2}.

Observer bias and variability between visits

Aimed at assessing the prevalence of terminal digit preference and the preference for therapeutic cutoff values, raw data of the VALTOP Trial (identified as study 1) were compared with the data based on AuscBPM, obtained in another recently performed double-blinded controlled parallel arm Valsartan Study (identified as study 2, VAST Study).

Results

Observer bias: comparison between data obtained in VALTOP (study 1, automated blood pressure measurements) and in the VAST Trial (study 2, conventional auscultatory blood pressure measurements)

From the 54 422 BP readings, the distributions of DBP and SBP readings obtained by eBPM in VALTOP (study 1) at all visits and at visit 2, that is, at the visit in which diagnostic criteria were applied to implement treatment

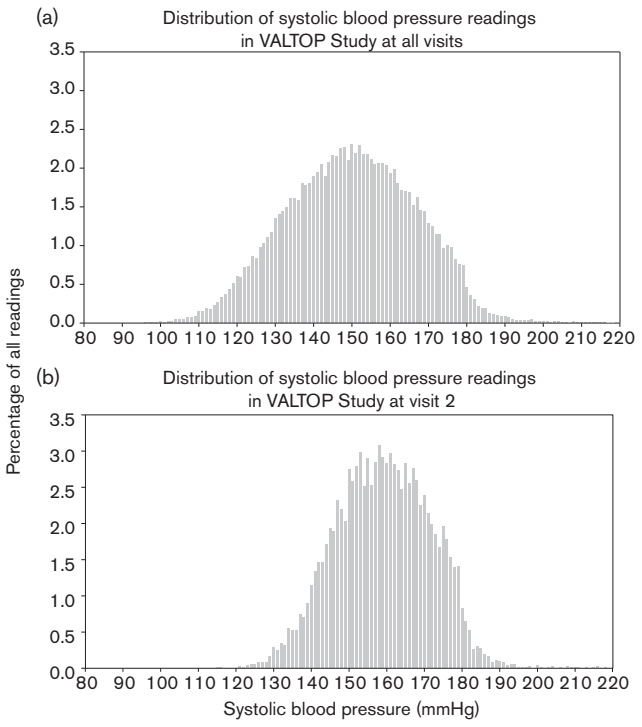
are shown in Figs 1 and 2. The distribution of the automated readings collected throughout the study has a Gaussian shape, that conversely cannot be seen in the VAST Trial (study 2), (23 062 individual readings) in which conventional sphygmomanometry was used (Figs 3 and 4). With conventional readings, a clear preference for BP values with digit '0' is observed (see frequency peaks at DBP values of 80, 90, 100 mmHg and at SBP values of 120, 130, 140, 150, 160 and 170 mmHg). A comparison of terminal digit preference between the two studies is shown in Table 1. Although conventional sphygmomanometry allows measuring BP to the nearest 2 mmHg, the prevalence of digits 1,3,5,7 and 9 was much higher than expected and this is particularly true for digit 5.

The distribution of SBP values at visit 3 in the VAST Trial (study 2), (3503 readings), that is, at a visit in which diagnostic thresholds were applied to identify patients eligible to continue in the study, is worth noting. Only patients with a mean SBP at least 160 mmHg (average of three individual readings) qualified to enter the next treatment phase. As shown in Fig. 3b, there was a striking preference for SBP values at or just above 160 mmHg with a very low prevalence for values less than 160 mmHg for each individual reading.

A closer look at the bias affecting BP measurements with regard to thresholds set to decide implementation of drug treatment is provided in Fig. 2b, Fig. 3b, Fig. 5. The cutoff value for treatment implementation was a DBP at least 95 mmHg in the VALTOP Trial (study 1) at visit V2 (11 997 readings), and a SBP at least 160 mmHg in the VAST Trial (study 2, conventional sphygmomanometry). In the latter study, the low prevalence of the SBP value of 158 mmHg contrasts sharply with the prevalence of BP values just above the 160 mmHg cutoff value. However, even with use of eBPM, in the VALTOP Trial a preference for BP values at or just above the cutoff values was observed as well.

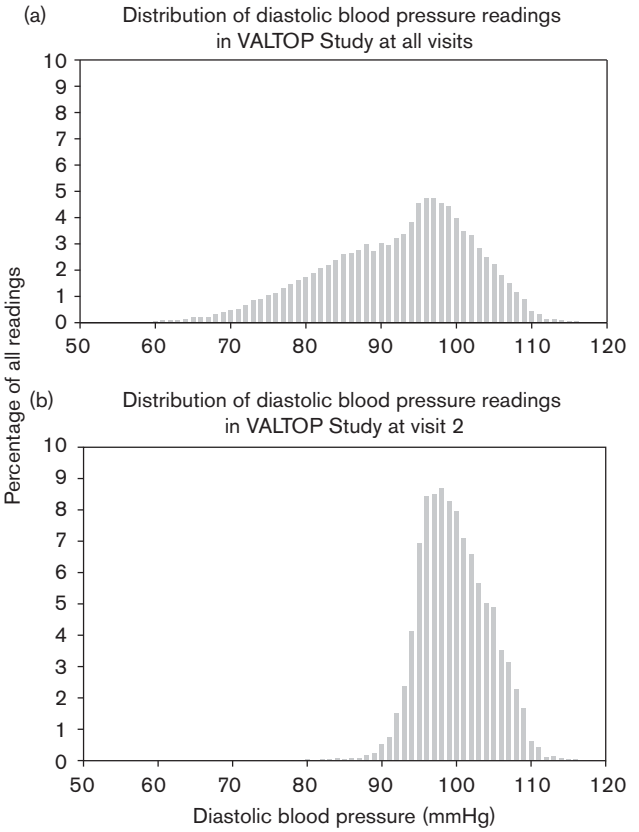
At the start of the open-label period (visit 2), all patients needed to have a mean seated DBP of at least 95 and 109 mmHg or less. The observer bias introduced by this criterion is shown in Fig. 2b, Fig. 5a.

Fig. 1



Distribution of systolic blood pressure readings in the VALTOP Study at all vistits (a) and at vistit 2 (b).

Fig. 2

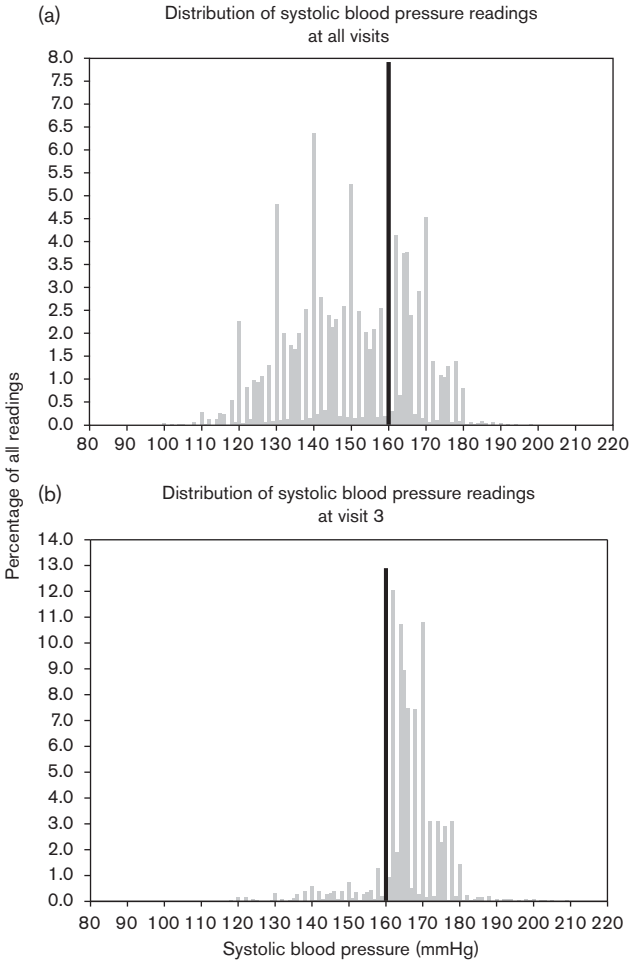


Distribution of diastolic blood pressure readings in the VALTOP Study at all visits (a) and at visit2 (b).

Variability of blood pressure measurements at each clinic visit and optimal method for collecting blood pressure readings

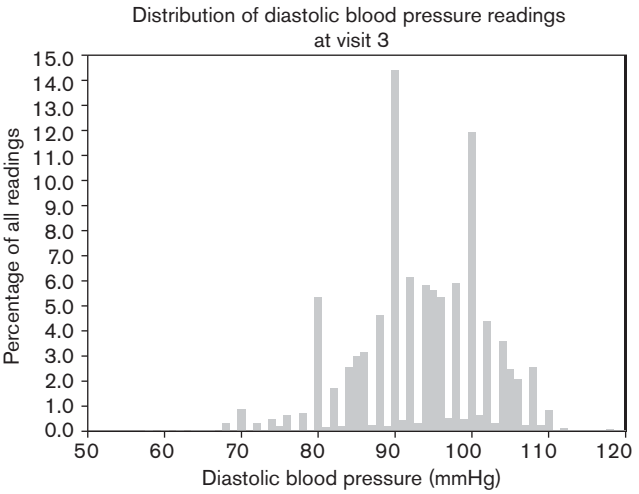
The results from the various simulations made to identify the best procedure aimed at reducing the variability of BP readings are summarized in Table 2, together with the assumptions made for each simulation.

Fig. 3



Distribution of systolic blood pressure readings in the VAST Study at all visits (a) and at visit 3 (b).

Fig. 4



Distribution of diastolic blood pressure readings in the VAST Study.

Table 1 Digit preference by investigators in the VALTOP Study (based on eBPM) and in study 2 (based on auscultatory readings, see Materials and methods)

	VALTOP (study 1)		VAST Trial (study 2)	
End digit	Diastolic %	Systolic %	Diastolic %	Systolic %
0	9.67	10.15	36.58	32.37
1	9.22	10.01	1.10	0.98
2	9.49	10.05	13.41	13.93
3	9.44	9.66	1.37	1.56
4	9.80	9.93	11.56	12.24
5	10.66	10.00	10.70	11.59
6	10.54	9.84	10.41	11.52
7	10.61	10.24	1.12	0.86
8	10.52	10.09	12.77	14.01
9	10.05	10.03	0.99	0.95

eBPM, electronic method for blood pressure measurement; VALTOP, Valsartan 320 mg EU Registration Study; VAST, valsartan study of similar design.

The reading error observed for strategy 4 was the lowest (within a SD approximately 1.55 mmHg), allowing the most precise estimate of treatment effect. However, strategy 4 requires more BP measurements to be taken (five measurements per patient). Strategy 2 has the advantage of combining a very simple procedure with an acceptable SD.

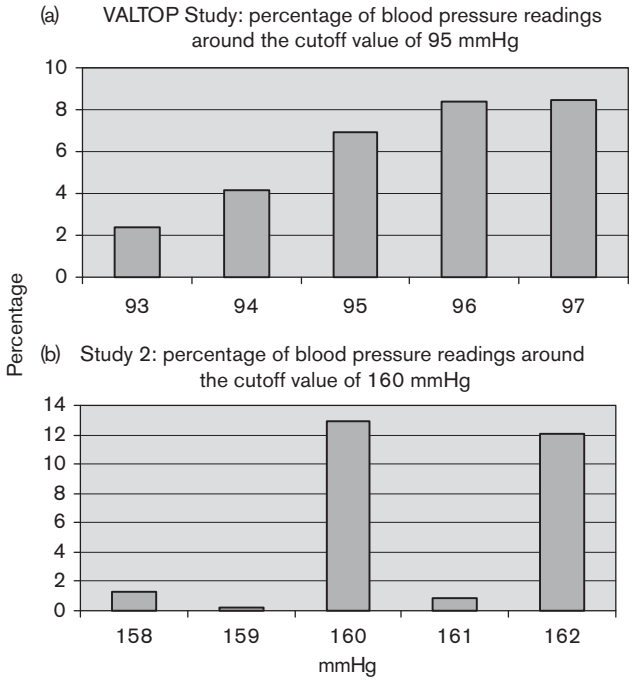
Discussion

The main finding of this study is that the use of eBPM, as compared with conventional sphygmomanometry, allowed reducing the bias associated with terminal digit preference and with preferences around specific BP cutoff levels identified as a guide to treatment decisions. Furthermore, the within-patient variability of three automated BP measurements taken during a single visit was low enough to allow achievement of a high statistical power in the VALTOP drug trial. This allowed the identification of statistically significant differences between the effects of valsartan 160 and 320 mg. These observations clearly show that eBPM can safely and effectively be used in clinical research as an alternative to AuscBPM [17].

Observer bias

The comparison of data from the VALTOP Trial with data obtained in the recent VAST Trial (study 2) based on AuscBPM, confirms and extends earlier observations on the important bias associated with the phenomenon of terminal digit preference and preferences at diagnostic or therapeutic cutoff values when using AuscBPM. Indeed, the most common source of bias in BP measurement is the preference for terminal digit '0'. Prevalence of digit '0' varies depending on the setting and the training of physicians or nurses, ranging from values of 86 [12] to 65–84 [18], 44 [11] and 33% [19]. The better the

Fig. 5



Blood pressure readings around cuttoff values in the VALTOP (a) and VAST Study (b).

Table 2 Variability of blood pressure measurements with different strategies for collecting blood pressure readings in VALTOP

Strategy	Reading error (mmHg)[a] Baseline	Endpoint	Between patients SD for Δ DBP (mmHg)[b]	Expected number of BP readings for each patient	Study power (%)[c]
1	2.20	2.16	7.62	3	87.6
2	1.89	1.86	7.42	3	88.9
3	1.89	1.86	7.42	4	88.9
4	1.56	1.54	7.32	5	90.0

Δ, mean differences; DBP, diastolic blood pressure; SD, standsrd deviation; VALTOP, Valsartan 320 mg EU Registration Study.
[a]Within-patient SD for DBP.
[b]Averaged over the population.
[c]Power calculation based on VALTOP expected difference in DBP = 1.2 mmHg.

observer's training the lower the terminal digit preference, a phenomenon already described as early as in 1968 by a study with nurses who had attended a 2-week training course to perform correct BP measurements [20]. Interestingly, such a bias was reported to occur even in a study with electronic, oscillometric home devices [21], probably because of the inaccuracy in the manual reporting of digital readings on the respective logbooks or Case Report Forms [22]. The latter procedure was also followed in the VALTOP Trial. In spite of this, the data obtained through the automated oscillometric readings performed in this trial clearly show that such a bias can be reduced as compared with the recent trials based on AuscBPM (VAST Trial, study 2). A similar favorable effect on observer bias with the use of automated devices has also been reported in a study carried out in both outpatient and inpatient settings [12]. The results of this study were so encouraging as to lead to the introduction of validated eBPM devices in the routine clinical activity of the Medizinische Poliklinik, Department of Internal Medicine at the University of Bonn.

Another important source of bias in BP measurement is associated with preferences when identifying therapeutic cutoff values, as observed in the study 2 based on AuscBPM and to a lesser extent also in the VALTOP Trial (Figs 3b and 5a). The same problem has also recently been shown to affect BP measurement aimed at defining BP levels around diagnostic cutoff values. This is exemplified by two trials in which a preference for the diastolic value of 80 mmHg was observed, that is, for a BP value considered to be the normality cutoff level [12,23]. As can be seen in Figs 2b, 5a, also with eBPM in the VALTOP Trial, the prevalence of DBP values at or just above 95 mmHg increased at V2, as this cutoff value was selected for patients' inclusion in the open-label treatment phase. To completely eliminate such a bias persisting even with eBPM, automated BP readings should probably be directly transferred to electronic Case Report Forms without any manual intervention by the observers. Such a procedure has also been proposed for BP values self-measured at home by patients because of the frequent unreliability of self-documented BP readings [1]. Manufacturers should thus develop devices that are able to allow for wireless data transfer and automated storage of individual readings.

Another interesting methodological issue addressed in our study concerned the best strategy aimed at reducing the differences in BP values within each measurement session, and thus at increasing the power of the study results. This was done through a simulation performed to identify what could be the optimal method for collecting reliable BP readings, reducing the likelihood of outliers (Table 2). Different strategies were tested on the standard set of three measurements defined in the study protocol. The reading error observed for strategy 4 was the lowest (with a SD within measurements of 1.54 mmHg). Adoption of this strategy, based on the performance of five measurements with exclusion of the highest and the lowest ones, seems to therefore theoretically guarantee the most precise estimate of treatment effect using one set of eBPM values. However, the gain in study power with this approach is relatively small and is counterbalanced by the inconvenience related to the need of taking more BP measurements (five per patient, i.e., 40% more than with strategy 2), which may reduce the compliance of the investigators and the patients with the study procedures. Therefore, taking all these considerations into account, the compromise reached in

strategy 2 (three consecutive measurements) seems to be preferable for clinical trials and in the physician's office, based on considerations focusing on both convenience and compliance.

These methodological issues should be carefully considered by manufacturers in the development of professional eBPM devices, as proposed by the European Working Group of Blood Pressure Measurement [24].

Limitations of the study

A clear limitation of our study is the lack of a direct head-to-head comparison of eBPM with AuscBPM in the same trial. We could only compare the VALTOP eBPM data with historical data available from the recent VAST Trial performed in a similar setting. Despite this limitation, however, such an analysis was able to show an impressive observer bias in AuscBPM trials, which was almost completely eliminated with eBPM. Another limitation of our study comes from the lack of a placebo arm, which did not allow us to prove the usefulness of eBPM and of other procedures implemented in the protocol, to select a truly hypertensive population and to reduce the possible interference by either a white coat or a placebo effect. This, however, does not reduce the interest of our data with regard to the use of eBPM in the setting of drug trials because it clearly shows the advantages associated with such an approach.

The primary efficacy variable for study 2 was the change in mean SBP to endpoint (week 24). This could lead to bias as conclusions from the VAST Trial (study 2) may not be applicable to all AuscBPM studies.

Implications

The conclusions of our study support the proposal that eBPM should replace standard sphygmomanometry in clinical trials. This suggestion is based on the results of our VALTOP Study and the recently published ASCOT, which made successful use of validated, automated BP measuring devices (ASCOT). This proposal is further supported by the evidence that automated BP measuring devices may also improve data analysis in epidemiological studies as compared with sphygmomanometric measurements by an aneroid device [25]. Further advantages of eBPM are represented by the need of less training for observers as compared with AuscBPM, and by the possibility of its use in countries in which mercury is banned. Further progress in the field could be represented by the possibility to automatically transfer recorded values to a personal computer in a digital format to minimize any residual bias during data filing. In the meantime, the use of BP measuring devices equipped with printing facilities may offer an acceptable solution to increase the reliability of data reporting from investigational sites.

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